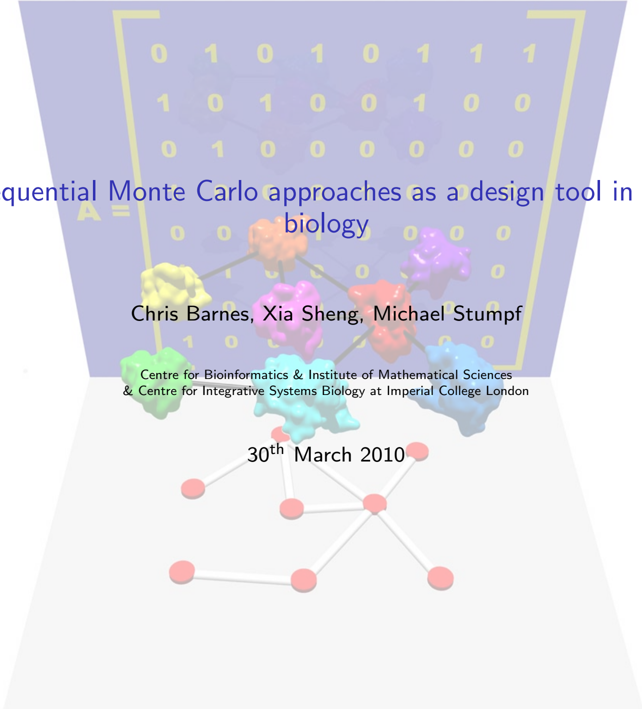

Using sequential Monte Carlo approaches as a design tool in synthetic biology

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Centre for Bioinformatics & Institute of Mathematical Sciences
& Centre for Integrative Systems Biology at Imperial College London

30th March 2010

Introduction

Synthetic genetic circuits

- Understand how organisms function

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- Produce drugs more effectively eg anti malarials
- Metabolize toxic chemicals
- Modify bacteria to hunt and kill tumors
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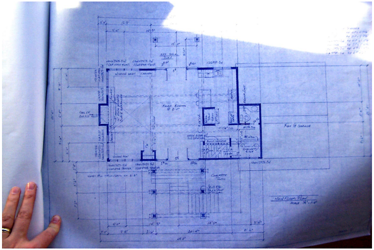
How do we design genetic circuits to perform these functions?

Synthetic biology vs Systems biology



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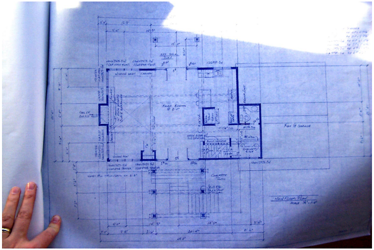

System design as an inference problem

Which configuration of components will give an output O given an input I?
Which model best describes the observed data O given conditions I?

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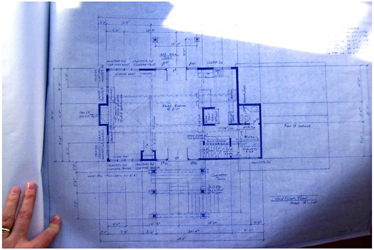

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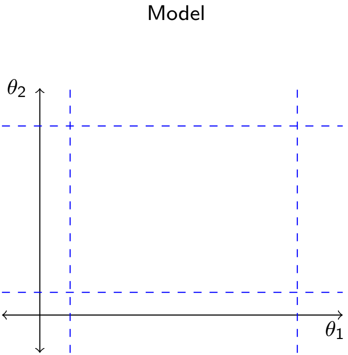
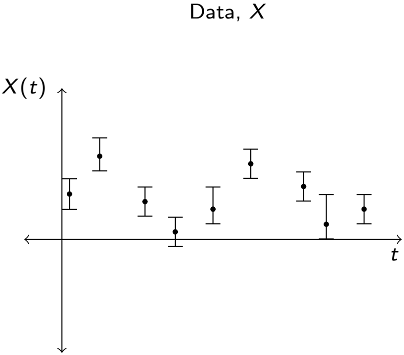
Advantages of using Bayesian framework for system design

- Credible limits on parameter values vs optimum values
- Model selection through Bayes factors
- Sensitivity from posterior distribution
- Incorporate prior biological knowledge into system design

Approximate Bayesian Computation





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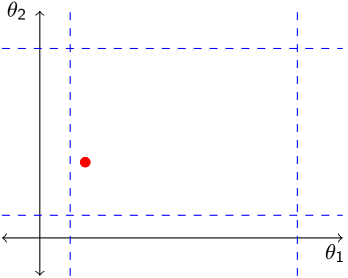

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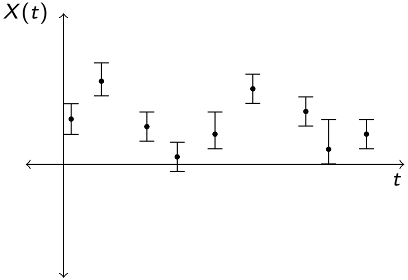

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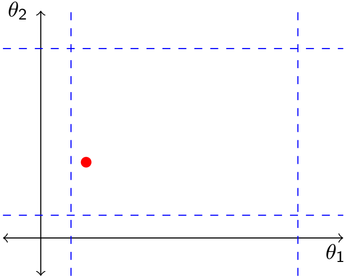

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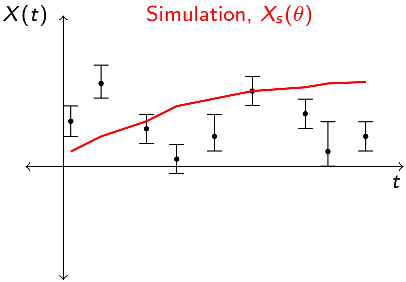

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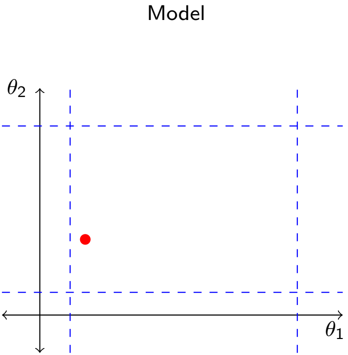

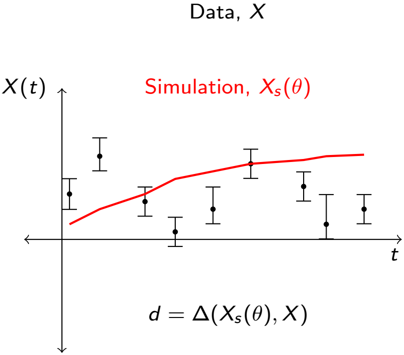

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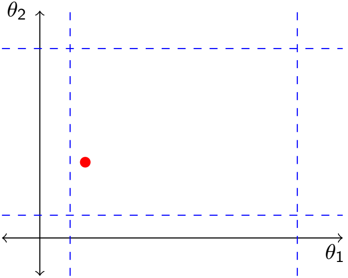

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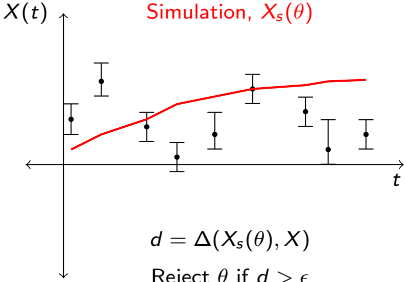

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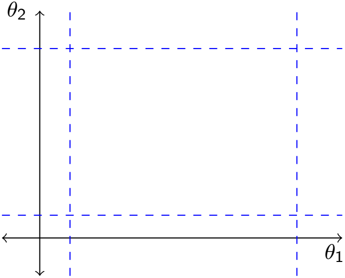

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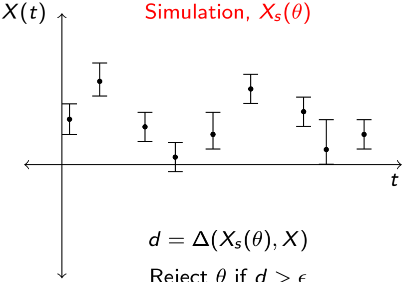

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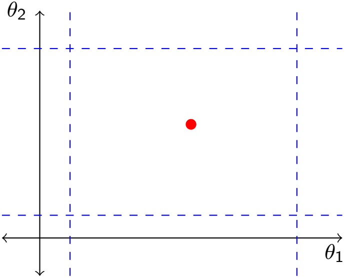

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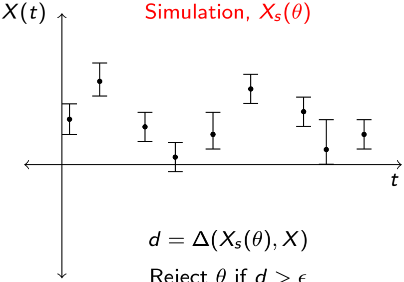

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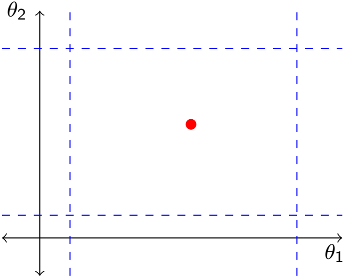

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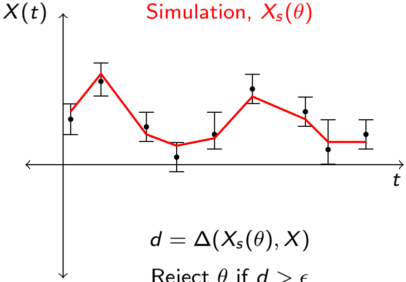

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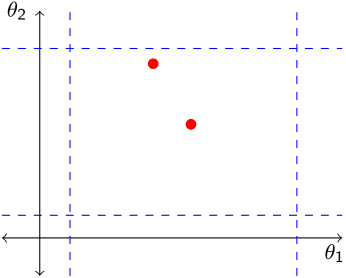

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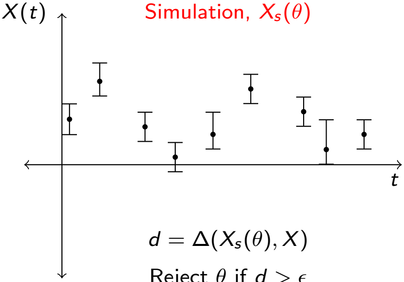

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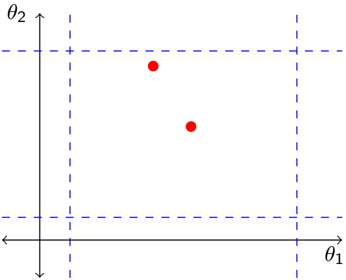

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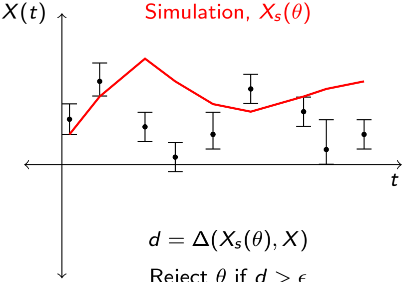

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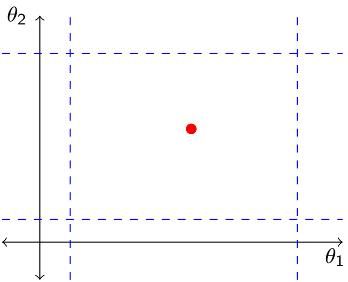

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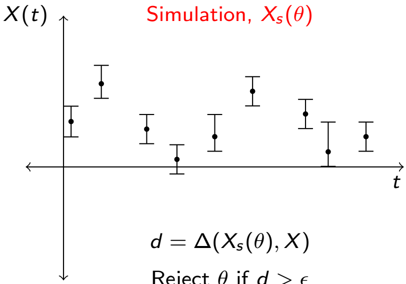

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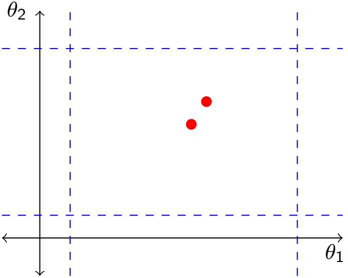

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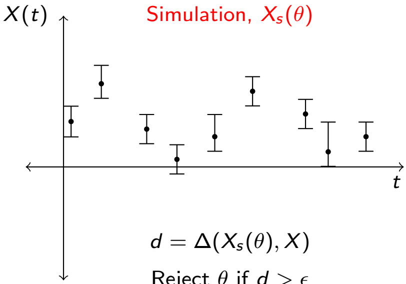

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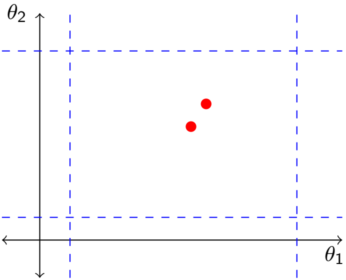

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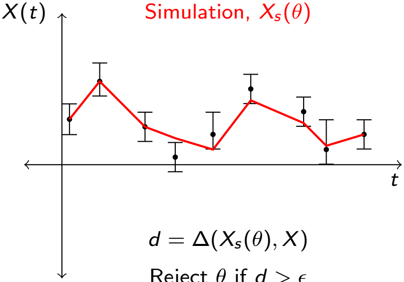

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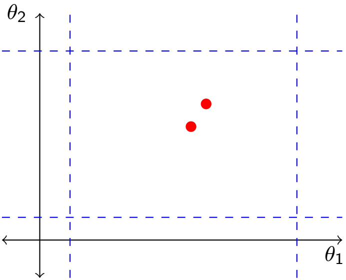

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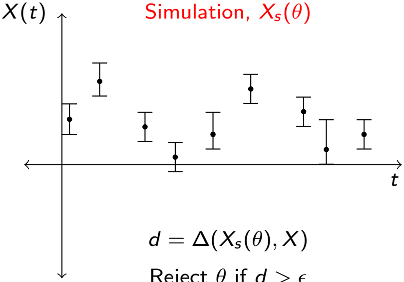

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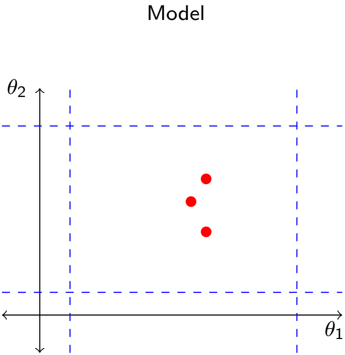

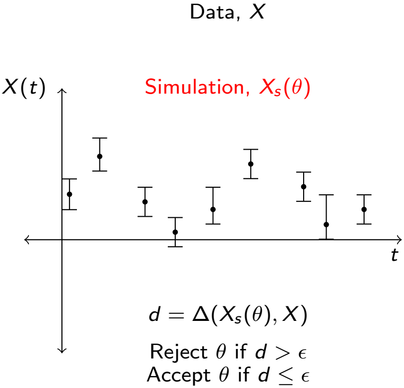

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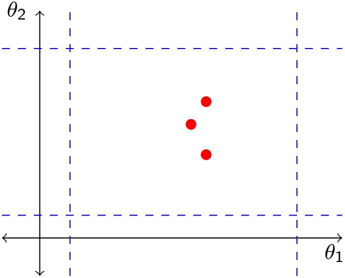

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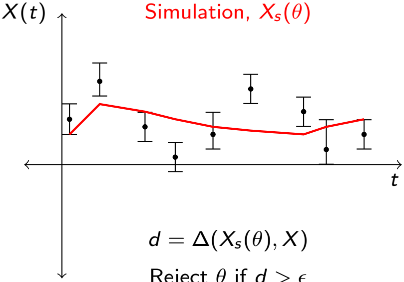

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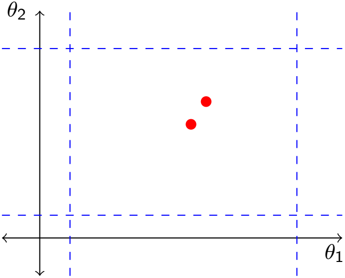

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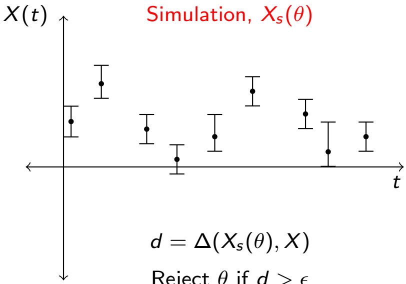

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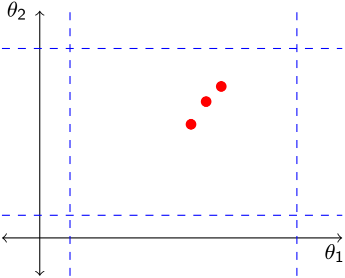

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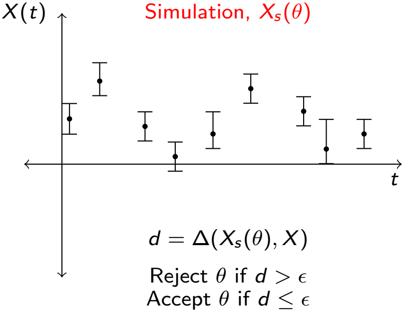

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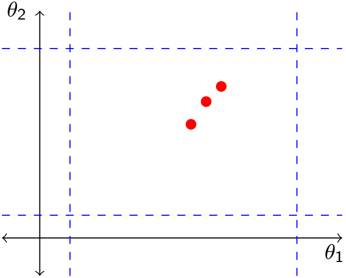

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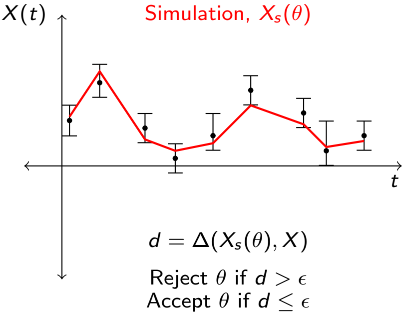

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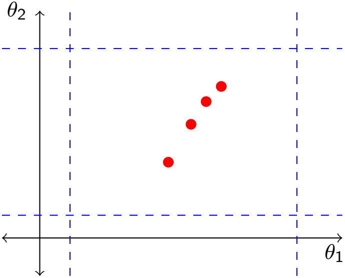

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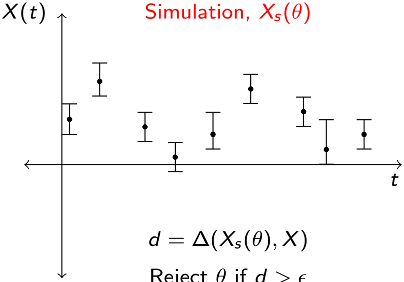

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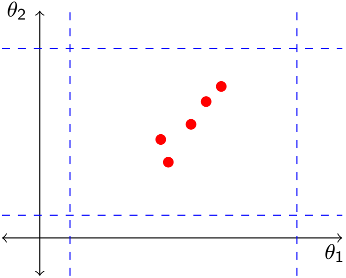

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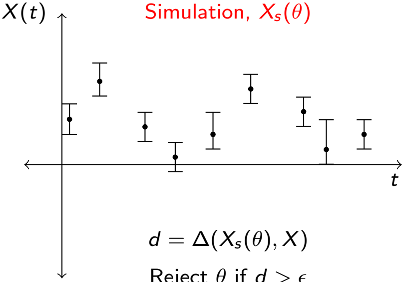

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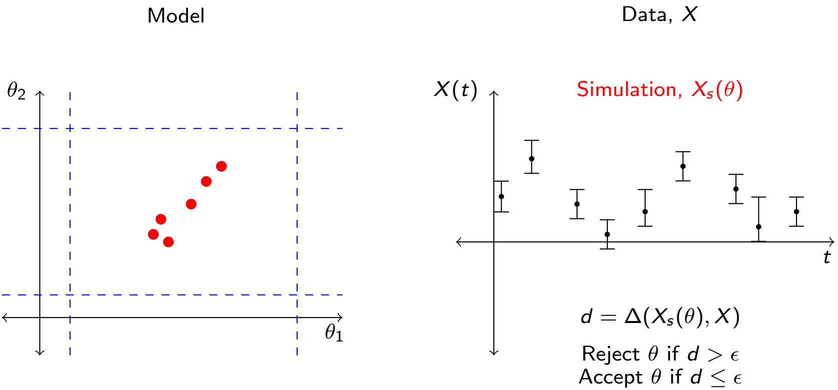

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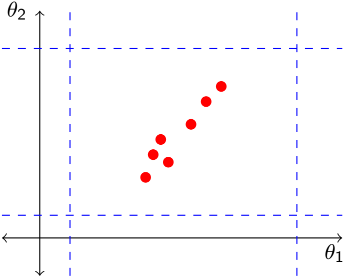

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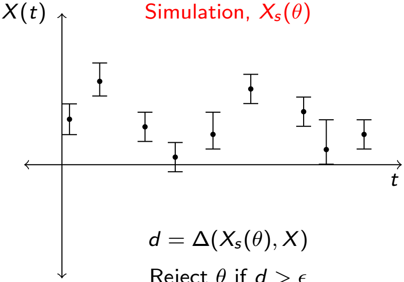

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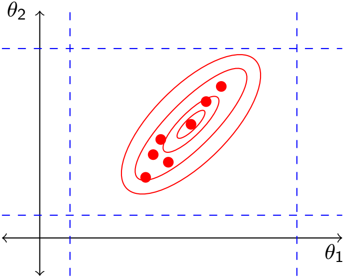

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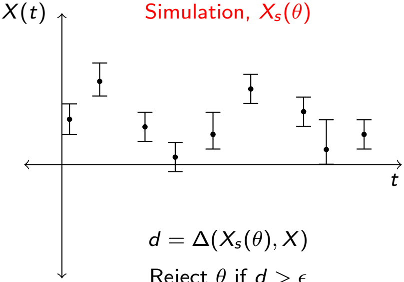

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Approximate Bayesian Computation (ABC)

Bayesian Inference

Posterior	$\propto$	Likelihood	$\times$	prior
$p(\theta\|X)$	$\propto$	$p(X\|\theta)$		$p(\theta)$

Approximate inference methods

Sample from approximate posterior:

$$p(\theta|\Delta(X_s(\theta), X) \leq \epsilon).$$

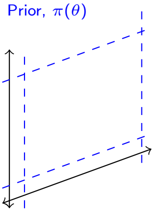
where $\Delta(X_s, X)$ is distance between simulation and data.
It can be shown, as $\epsilon \longrightarrow 0$

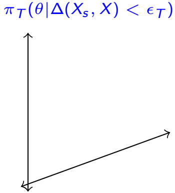
$$p(\theta|\Delta(X_s(\theta), X) \leq \epsilon) \longrightarrow p(\theta|X)$$

ABC flavours

- ABC rejection Pritchard *et al.* Mol. Biol. Evol. (1999)
- ABC MCMC Marjoram *et al.* PNAS (2003)
- ABC SMC Toni and Stumpf, Bioinformatics (2010)

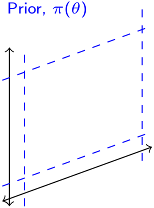
ABC SMC





ABC SMC

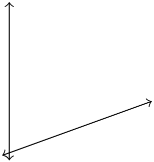
Prior, $\pi(\theta)$



Define set of intermediate distributions, π_t, $t = 1, \ldots., T$

$$\epsilon_1 > \epsilon_2 > \ldots\ldots > \epsilon_T$$

$\pi_{t-1}(\theta|\Delta(X_s, X) < \epsilon_{t-1})$



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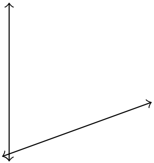

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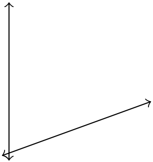

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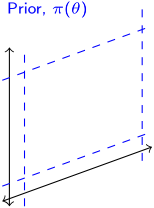

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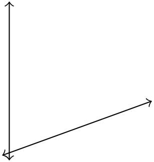

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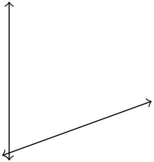

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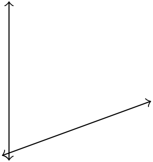

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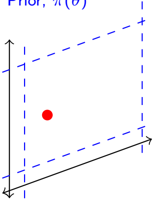

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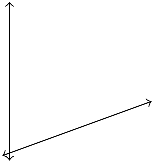

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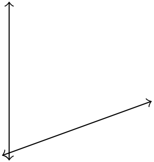

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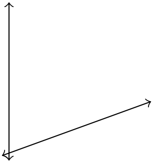

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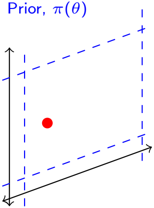

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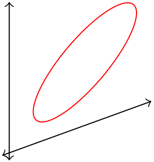

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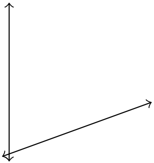

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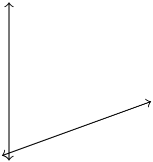

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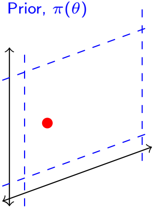

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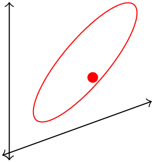

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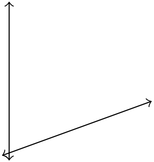

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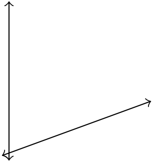

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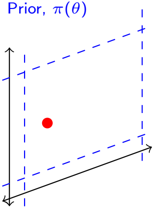

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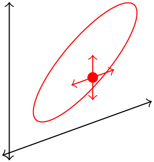

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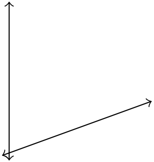

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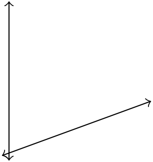

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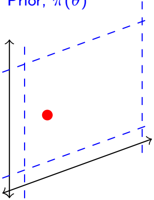

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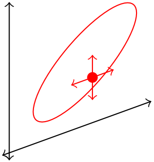

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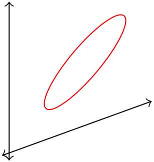

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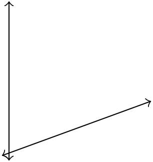

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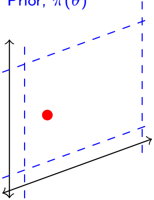

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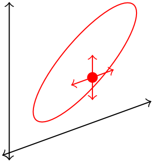

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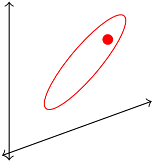

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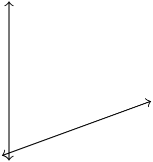

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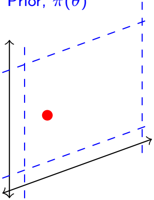

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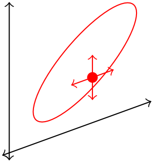

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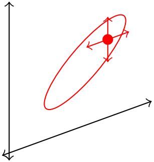

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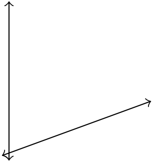

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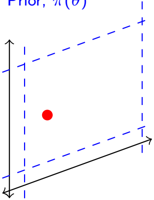

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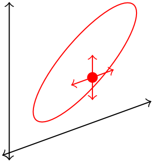

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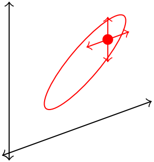

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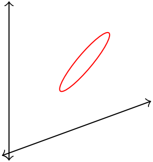

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- TCSs are abundant in bacteria, plants and fungi, but apparently absent from animals.
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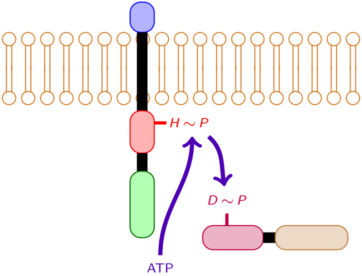

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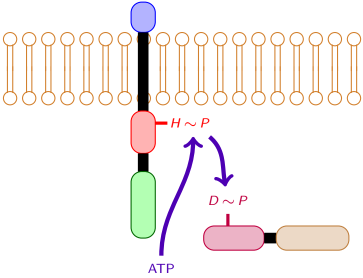
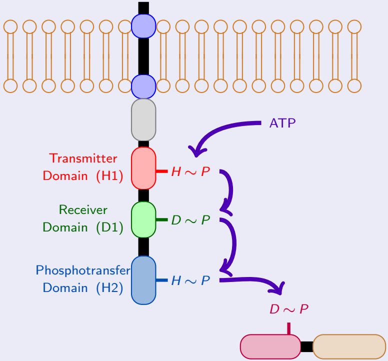


The ArcB-ArcA TCS

The ArcB-ArcA system in *Escherichia coli* uses a phospho-relay mechanism.



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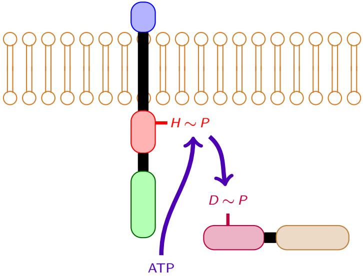

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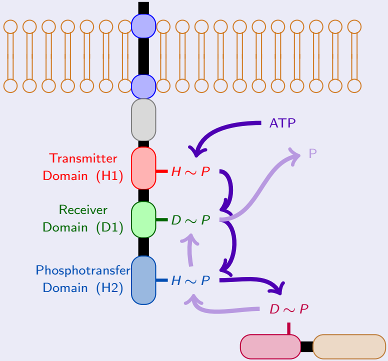

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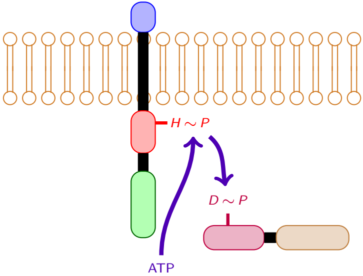

Orthodox system

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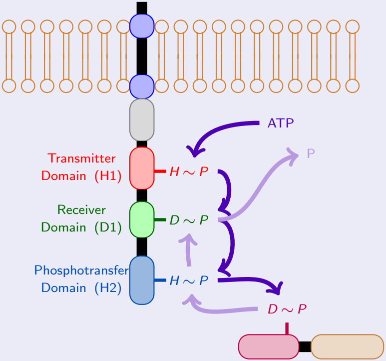
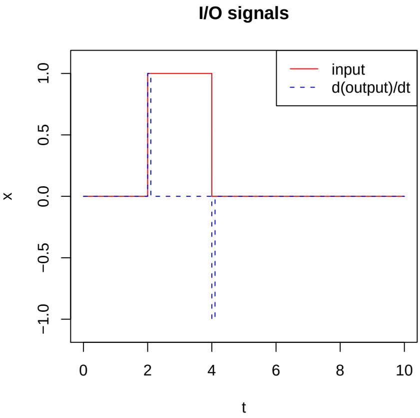
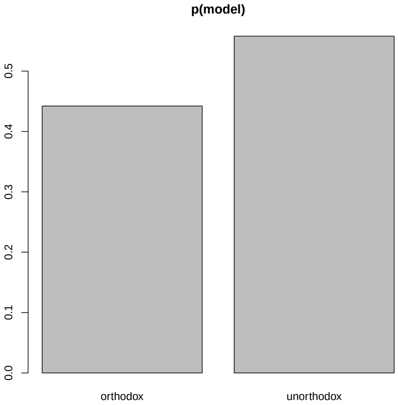


Unorthodox system

Example1 : Fast response





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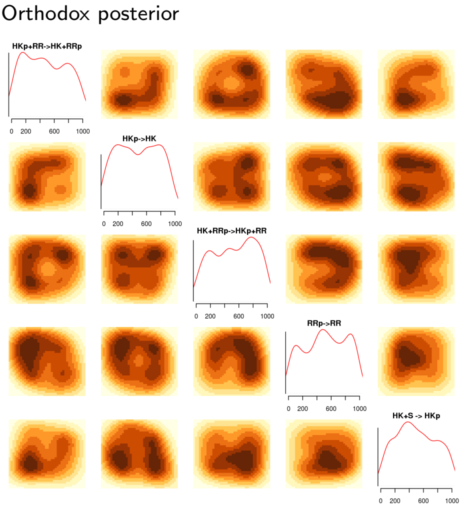
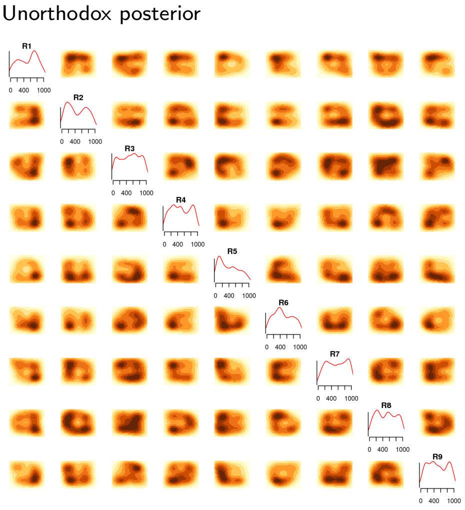
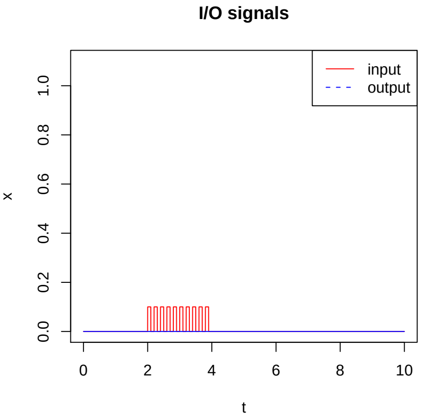
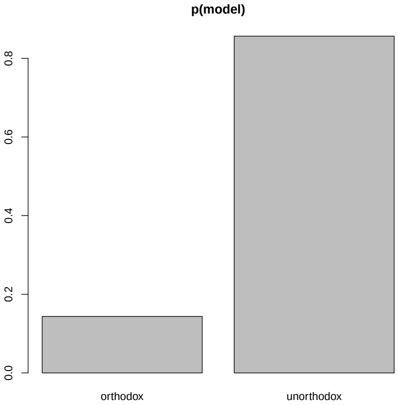




R1: $x \bullet \bullet \longrightarrow o \bullet \bullet$, R2: $ox\bullet \longrightarrow xo\bullet$, R3: $\bullet ox \longrightarrow \bullet xo$, R4: $\bullet \bullet o + RR \longrightarrow \bullet \bullet x + RRp$, R5: $\bullet xo \longrightarrow \bullet ox$ R6: $\bullet o \bullet \longrightarrow \bullet x \bullet$, R7: $\bullet \bullet x + RRp \longrightarrow \bullet \bullet o + RR$, R8: $o \bullet \bullet \longrightarrow x \bullet \bullet$, R9: $RRp \longrightarrow RR$

Example2 : Robust to noise





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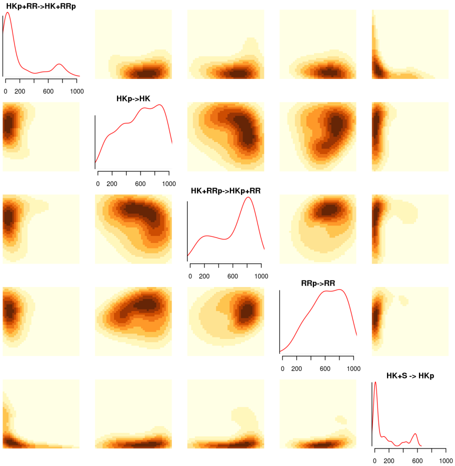

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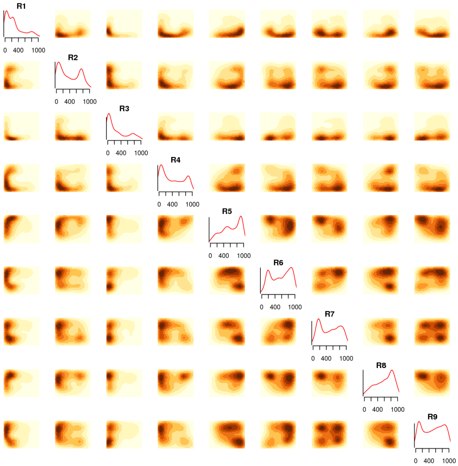

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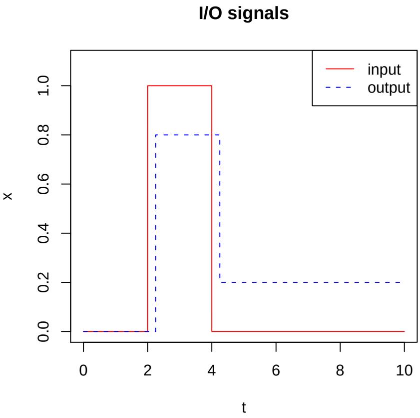
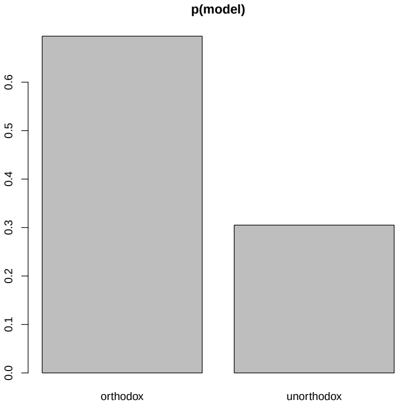
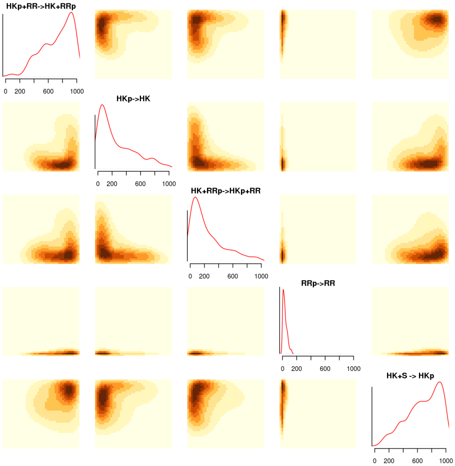
Example3 : Fast response, high maximum, low minimum



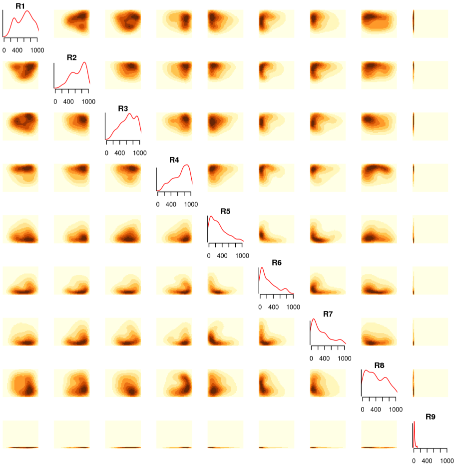


Example 3: posteriors

Orthodox posterior

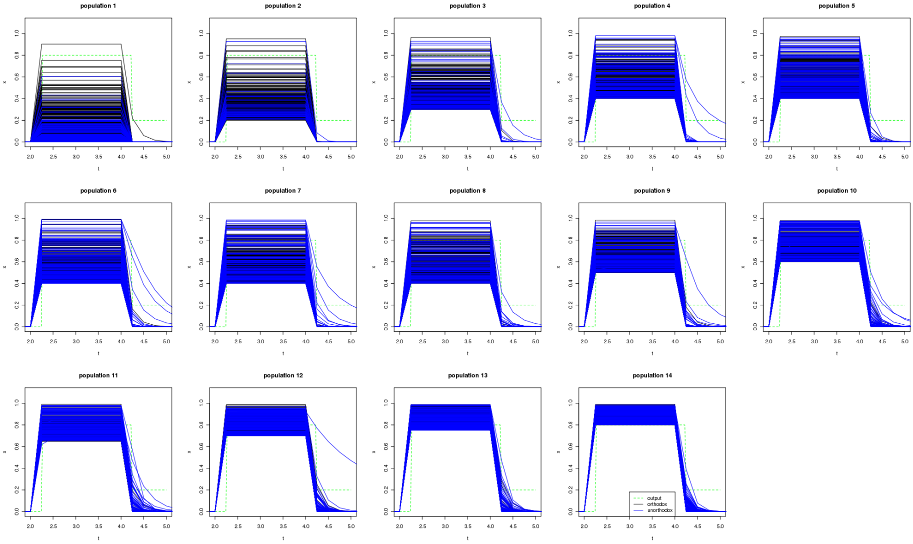


Unorthodox posterior



R1: $x \bullet \bullet \longrightarrow o \bullet \bullet$, R2: $ox\bullet \longrightarrow xo\bullet$, R3: $\bullet ox \longrightarrow \bullet xo$, R4: $\bullet \bullet o + RR \longrightarrow \bullet \bullet x + RRp$, R5: $\bullet xo \longrightarrow \bullet ox$ R6: $\bullet o \bullet \longrightarrow \bullet x \bullet$,
R7: $\bullet \bullet x + RRp \longrightarrow \bullet \bullet o + RR$, R8: $o \bullet \bullet \longrightarrow x \bullet \bullet$, R9: $RRp \longrightarrow RR$

Example 3: Trajectory evolution

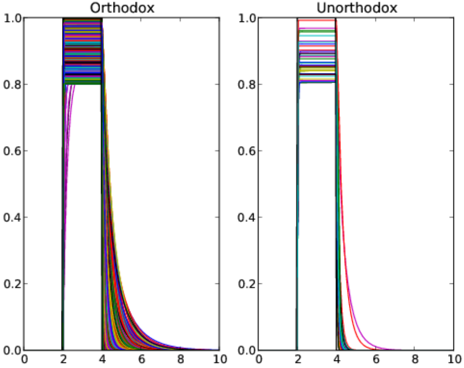


Example 3: Comparison to sensitivity analysis

Two approaches

- Examine region around optimum
- Sample uniformly from the prior

2060/10000	39/10000
0.981	0.019

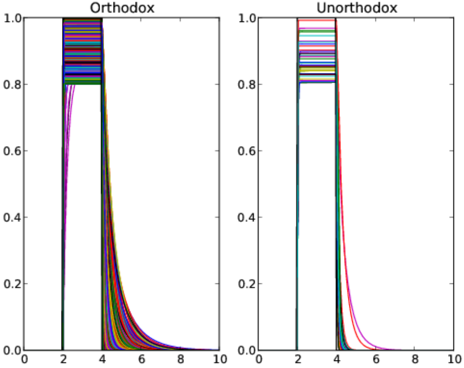


Example 3: Comparison to sensitivity analysis

Two approaches

- Examine region around optimum May miss alternative parameter combinations
- Sample uniformly from the prior

2060/10000	39/10000
0.981	0.019

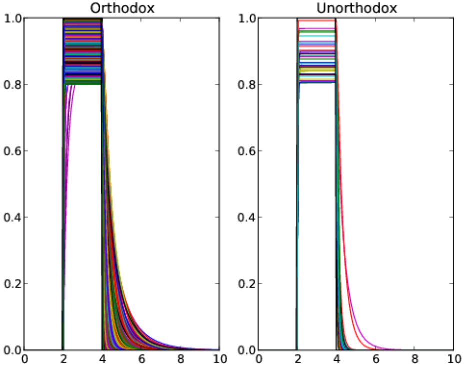


Example 3: Comparison to sensitivity analysis

Two approaches

- Examine region around optimum May miss alternative parameter combinations
- Sample uniformly from the prior May miss important regions

2060/10000	39/10000
0.981	0.019



Future work

BioBricks^{TM}

- Use selected BioBricks components to design genetic circuits and make predictions of behaviour under perturbations
- Build the circuit to test predictions

Genetic Design Automation (GDA)

- Genetic equivalent of Electronic Design Automation (EDA)
- Build complex genetic circuits and DNA sequence automatically from standard set of building blocks
- Engineering Genetic Circuits, Myers (2009)

Distant future

Using biological circuits to influence electronic circuit design

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